# REMARKS

## Status of the Claims

Claims 34-64 and 67-73 were considered in the non-final Office action mailed on January 29, 2007. As reflected in the listing of claims beginning on page 7 of this paper, Applicants amend claims 34, 63, 67 and 68 herein and add new claims 79 and 80. Support for the amendments to claims 34, 63, 67 and 68 and new claims 79 and 80 can be found in the specification and claims as originally filed, including at least at paragraphs [0060]-[0061] and [0063]-[0094]. Applicants submit that no new matter is introduced by the amendments and new claims. Claims 71 and 72 are canceled herein without prejudice to later reintroducing their subject matter. Following entry of the amendments, claims 34-64, 67-70, 73 and 79-80 will be pending for the Examiner's consideration.

## Amendments to the Specification

Applicants amend paragraphs [0043], [0055], [0172] and [0185] of the specification to remove hyperlinks and to correct the use of trademarks. Applicants submit that the amendments to the specification introduce no new matter.

## Objections to the Specification

The Office action objected to the specification as containing embedded hyperlinks and the use of trademarks. Applicants amend paragraphs [0043], [0055], [0172] and [0185] of the specification herein to remove hyperlinks and to correct the use of trademarks. Applicants submit that the amendments to the specification obviate the objections and respectfully request reconsideration and withdrawal of the objections.

## Summary of the Claimed Invention

The core of the present invention is the discovery that mutations in the MRP6 gene are associated with PXE. The genomic sequence of the MRP6 gene is provided in the specification at SEQ ID NO:1 and Applicants provide extensive clinical and biochemical evidence throughout

the specification supporting the conclusion that several specific mutations in the MRP6 gene are associated with PXE.

Amended independent claim 34 is directed to a method for detecting whether a mutation in an MRP6 gene is a PXE mutation by interrogating an MRP6 nucleic acid in a patient for the presence of a mutation, determining if the mutation is a co-segregator with a PXE phenotype, and identifying the patient as having a PXE mutation if a mutation is present in the MRP6 nucleic acid and the mutation is a co-segregator with the PXE phenotype.

Amended independent claims 63, 67, 68 and 73 are directed to methods of screening a patient for the presence of a PXE mutation, for a risk of having children with PXE, for a risk of developing a PXE associated symptom, and for the presence of a PXE mutation, respectively. According to these methods, an MRP6 nucleic acid in a patient sample is interrogated for the presence of a mutation known to be a co-segregator with a PXE phenotype and identifying the patient as having said mutation or said risk if the mutation or allele is detected in the MRP6 nucleic acid.

New independent claim 79 is directed to a method for detecting a patient having an increased risk of developing PXE by interrogating an MRP6 nucleic acid of the patient and determining an abnormal presence or absence of at least one nucleic acid fragment or sequence in the patient's MRP6 nucleic acid compared to a normal control.

New independent claim 80 is directed to a method for screening a patient for the presence of a MRP6 gene mutation in an individual having an increased risk of developing PXE. This method comprises in part interrogating an MRP6 nucleic acid in a patient sample to determine an MRP6 nucleic acid sequence and comparing the MRP6 nucleic acid sequence from step a) to a normal MRP6 nucleic acid sequence.

**Rejections Under 35 U.S.C. § 112, First Paragraph: Written Description**

Claims 34-38, 41-63 and 67-72 were rejected under 35 U.S.C. § 112, First Paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner alleges that the specification does not disclose and fully characterize the genus of interrogating

an MRP6 nucleic acid for the presence of any mutation that may or may not be associated with PXE. See, Office action at 2-4.

Applicants respectfully submit that the specification fully discloses the invention of the claims as amended. As the Examiner acknowledges on page 3 of the Office action, the specification teaches that PXE mutations map to the MRP6 genetic locus (see, *e.g.*, paragraph [0032]), and that several specific mutations associated with PXE are located at specific positions in the MRP6 genetic locus (see, *e.g.*, paragraphs [0034]-[0055]).

Applicants' specification also teaches that PXE mutations can be detected in a patient by establishing that a mutation in an MRP6 gene is a co-segregator with a PXE phenotype, as recited in claim 34. Specifically, Applicants teach a variety of methods for detecting mutations in the MRP6 gene including but not limited to single strand conformation polymorphism (SSCP) analysis, heteroduplex analysis (HA), and conformation-sensitive gel electrophoresis (CSGE). See, *e.g.*, paragraphs [0037] and [0149]-[0163]. Applicants further teach methods to determine if a mutation is a co-segregator with a PXE phenotype using multi-generational pedigree analysis. See, *e.g.*, paragraphs [0182]-[0185].

Applicants respectfully submit that, contrary to the assertion on page 4 of the Office action, the invention as claimed in amended claim 34 does not require knowledge of all contemplated PXE mutations. Instead, the invention as claimed is a method for determining if a detected MRP6 gene mutation is a PXE mutation. Specifically, the claimed invention is a method for detecting an MRP6 nucleic acid mutation and determining if the mutation is a co-segregator with a PXE phenotype. If the patient has an MRP6 mutation and if that mutation is a co-segregator with a PXE phenotype, the patient is identified as having a PXE mutation. This method is fully disclosed in the specification, as discussed in the preceeding paragraph. According to this method, the skilled artisan need not have prior knowledge of the specific mutation in order to determine that the MRP6 gene mutation is a PXE mutation.

Applicants further teach that the identification of any mutation of the MRP6 genetic locus can be used as a positive diagnosis of an increased risk of developing PXE, of developing PXE associated symptoms, or of having children who develop PXE, as recited in claims 63, 67, 68,

73, 79 and 80. See, *e.g.*, paragraphs [0060] and [0061]. Specifically, the specification teaches that the identification of the presence of any mutation in the MRP6 genetic locus is associated with having an increased risk of PXE (see, *e.g.*, paragraphs [0060] and [0061]). Although the specificity of the mutation results in differing risk of developing PXE and differing severity of PXE associated symptoms, the identification of the specific mutation is not necessary to diagnose a patient as having an increased risk of developing PXE (see, *e.g.*, paragraphs [0046], [0058], [0060] and [0061]).

Additionally, the specification teaches various methods for identifying a mutation, an abnormal presence or absence of at least one nucleic acid fragment or sequence, in the patient's MRP6 nucleic acid compared to a normal control MRP6 nucleic acid. See, *e.g.*, paragraphs [0064]-[0094], paragraphs [0147]-[0168] of Example 1, and paragraphs [0191]-[0207] of Example 6.

For at least the above reasons, Applicants respectfully submit that the present application fully complies with the written description requirement with respect to amended independent claims 34, 63, 67 and 68, their dependent claims 35-38, 41-62 and 69-70 and new independent claims 79 and 80 and request reconsideration and withdrawal of the rejections of claims 34-38, 41-63 and 67-72 under 35 U.S.C. § 112, First Paragraph.

**Rejections Under 35 U.S.C. § 112, First Paragraph: Enablement**

Claims 34-63 and 67-72 were rejected under 35 U.S.C. § 112, First Paragraph, as allegedly failing to enable one skilled in the art to make and/or use the invention without undue experimentation. Specifically, the Examiner alleges that, although the specification teaches several specific PXE mutations, the specification does not enable interrogating an MRP6 nucleic acid for the presence of any PXE mutation. Therefore, according to the Examiner, one of ordinary skill in the art would need to undertake undue experimentation and test hundreds, if not thousands, of possible nucleotide alterations thoughout the MRP6 gene to determine which mutations are PXE mutations. See, Office action at pages 4-8.

Applicants submit that the present specification fully enables one of skill in the art to determine if a mutation in an MRP6 gene is a co-segregator with a PXE phenotype as recited in independent claims 34 and 63. The specification of the present application provides reasonable guidance or direction on how to practice the claimed invention. For example, the specification teaches a variety of methods for detecting mutations in the MRP6 gene, *e.g.*, at paragraphs [0037] and [0149]-[0163]. The specification further teaches methods to determine if a mutation is a co-segregator with a PXE phenotype using multi-generational pedigree analysis, *e.g.*, at paragraphs [0182]-[0185]. One of skill in the art upon review of the recited paragraphs would readily have understood how to carry out nucleic acid assays and co-segregation analysis in order to determine if a mutation in an MRP6 gene co-segregates with a PXE phenotype.

Applicants submit that the present specification fully enables one of skill in the art to determine a mutation, abnormal presence or absence of at least one nucleic acid fragment or sequence, in a patient's MRP6 gene compared to a normal control as recited in independent claims 67, 68, 79 and 80. First, the specification of the present application provides reasonable guidance or direction on how to practice the claimed invention. For example, the specification teaches various nucleic acid analysis methods at paragraphs [0064]-[0094], paragraphs [0147]-[0168] of Example 1, and paragraphs [0191]-[0207] of Example 6. One of skill in the art upon review of the recited paragraphs would readily have understood how to carry out nucleic acid assays and to compare the assay results to a normal control in order to determine a mutation, abnormal presence or absence of at least one nucleic acid fragment or sequence, in the MRP6 gene.

Second, Applicants submit that all of the methods needed to detect abnormal presence or absence of a nucleic acid fragment or sequence in the MRP6 gene were well known in the art when the application was filed. In the art of molecular biology when this application was filed, it was routine for one of ordinary skill in the art to isolate nucleic acids from a patient sample, to conduct a nucleic acid assay such as hybridization or sequencing, to determine nucleic acid or protein fragment patterns or sequences, and to compare the determined patterns or sequences to normal controls in order to detect a presence or absence of abnormal fragment or sequence.

Applicants submit that experimentation, particularly when routine and thoroughly disclosed, is permissible. The court in *In re* Wands stated that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,'not 'experimentation.'" 858 F.2d 731, 736-737 (Fed. Cir. 1988). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely rountine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. at 737. Applicants submit that because (1) the disclosure teaches considerable direction and guidance on how to practice the invention, (2) the disclosure teaches several working examples, (3) there was a high level of skill in the art at the time when the application was filed, and (4) all of the methods needed to practice the invention were disclosed or well known, undue experimentation is not required to practice the claimed invention.

Thus, in view of the teachings of the present application and armed with the knowledge available in the art, one of ordinary skill readily would have been able to detect a PXE mutation in a patient by establishing if a mutation in an MRP6 gene is associated with PXE by determining if a mutation is a co-segregator with a PXE phenotype and to detect a patient who is more likely to develop PXE than a normal patient by determining abnormal presence or absence of at least one nucleic acid fragment or sequence in the patient's MRP6 gene compared to a normal control.

Applicants further submit that the knowledge of a specific mutation in the MRP6 gene is not required to practice the invention as recited in amended and new independent claims 67, 68, 79 and 80. Claims 67, 68, 79 and 80 are directed to a method for detecting a patient having an increased risk of developing PXE. In other words, claims 67, 68, 79 and 80 only require detecting a patient who is more likely to develop PXE than a normal patient. Applicants submit that claims 67, 68, 79 and 80 do not require detecting a specific mutation in a patient's MRP6 gene in order to determine that the patient is more likely to develop PXE than a normal patient. Detection of a mutation manifested by at least one abnormal nucleic acid fragment or sequence in a patient's MRP6 gene would be sufficient to indicate that the patient is more likely to develop

PXE than a normal patient because an MRP6 gene containing an abnormal nucleic acid fragment or sequence is more likely to have an abnormal MRP6 protein compared to a normal MRP6 gene. Similar correlation between defects in genes without knowledge of the specific mutation and disease is known in the medical arts. For example, it is well accepted that an individual is more likely to develop cancer than a normal individual if the individual's p53 gene (tumor suppressor gene) contains a mutation (*i.e.*, abnormal nucleic acid fragment or sequence) compared to a normal control, even if the specific nature of the mutation is unknown.

Therefore, Applicants submit that the nature of the invention as claimed in amended and new independent claims 67, 68, 79 and 80 does not require the knowledge of a specific mutation. It only requires determination of abnormal presence or absence of at least one nucleic acid fragment or sequence in a patient's MRP6 gene compared to a normal control.

For at least the above reasons, Applicants respectfully submit that the present application fully complies with the enablement requirement with respect to amended independent claims 34, 63, 67 and 68, their dependent claims 35-62, 64 and 69-70 and new independent claims 79 and 80 and request reconsideration and withdrawal of the rejections of claims 34-63 and 67-72 under 35 U.S.C. § 112, First Paragraph.

**Double Patenting Rejection**

Claims 34-64 and 67-73 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,780,587. Applicants will present a Terminal Disclaimer once one or more claims are found allowable, disclaiming the terminal part of any patent granted on U.S. Serial No. 10/764,328 which would extend beyond the full statutory term of U.S. Patent No. 6,780,587. Applicants submit that the filing of a Terminal Disclaimer will obviate the double patenting rejection and respectfully request reconsideration and withdrawal of the rejection.

## Conclusion

In view of the foregoing remarks, Applicants respectfully request allowance of claims 34-64, 67-70 and 73. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite allowance of this application, the Examiner is cordially invited to call the undersigned attorney.

Respectfully submitted,

Date: April 25, 2007
Reg. No. 58,343

Karen A. Schouten
Attorney for Applicant(s)
Kirkpatrick & Lockhart Preston
Gates Ellis LLP
State Street Financial Center
One Lincoln Street
Boston, Massachusetts 02111-2950

Tel. No.: (617) 261-3216
Fax No.: (617) 261-3175